News Update: A New PD Gene; More Discoveries and a Mystery

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At the beginning of 2003, Vincenzo Bonifati, Peter Heutink and colleagues published the discovery of a new gene that causes Parkinson's disease in two very rare families from isolated populations (see news). Before the significance for human disease had been identified, this same DJ-1 gene had been isolated in several laboratories around the world, but had remained obscure, of interest mainly to people working on reproduction. From the first report in 1997 until the end of 2002 when the connection to PD was made there were only 10 scientific publications on DJ-1. In contrast, during the nine months since the publication by Bonifati *et al.,* there have been 16 papers or commentaries on this small protein. This shows how much identification of a new mutation can accelerate the pace of research on a specific gene. In the past, these kinds of discoveries have also led to dramatically increased interest in the diseases under study—and in many cases have led to a much greater understanding of what actually "causes" the diseases in both inherited and more common non-inherited forms.

What has been done in different laboratories, and what can we learn from these studies? There are three major pieces of information that have rapidly been elucidated. Firstly, several labs including ours (Hague et al., 2003) have looked for other cases with mutations in the same gene. Reports of these gene-screening studies are still coming in and it is too early to be sure about exactly how many people will have mutations in this gene. What is clear is that DJ-1 mutations are relatively rare: less common than, for example, mutations in parkin, another recessive gene that causes a very similar disease.

Secondly, we now have a fairly precise model of the protein, as several independent groups have produced the protein in purified form and subjected it to a process called x-ray crystallography. Proteins are produced as a string of building blocks called amino acids, but to function properly they are folded into intricate 3D structures. This allows us to look at the location of specific residues within the structure and we have concentrated on those that cause disease when there is a single change (a point mutation). The picture (based on data generated by Mark Wilson and colleagues; Wilson et al., 2003) shows two mutations that have been found which happen to be close to each other in the model. As more mutations are found, we will begin to see if a general pattern emerges.

The third piece of news is that we are starting to understand how these small mutations produce disease. From the first report, it was clear that some mutations are very simple: a deletion of part of the DNA that contains the gene for DJ-1 means that there is no protein produced within cells. It turns out that the point mutations probably work in a similar way. The protein is unstable and is rapidly cleared from cells, which have a specific machinery designed for this purpose (Miller et al., 2003). This means that the point mutations and the large deletion cause disease in the same way—by decreasing the amount of protein in the cell its normal function is lost. The mystery is what this normal function is. The challenge now is to understand why the loss of this function damages neurons.

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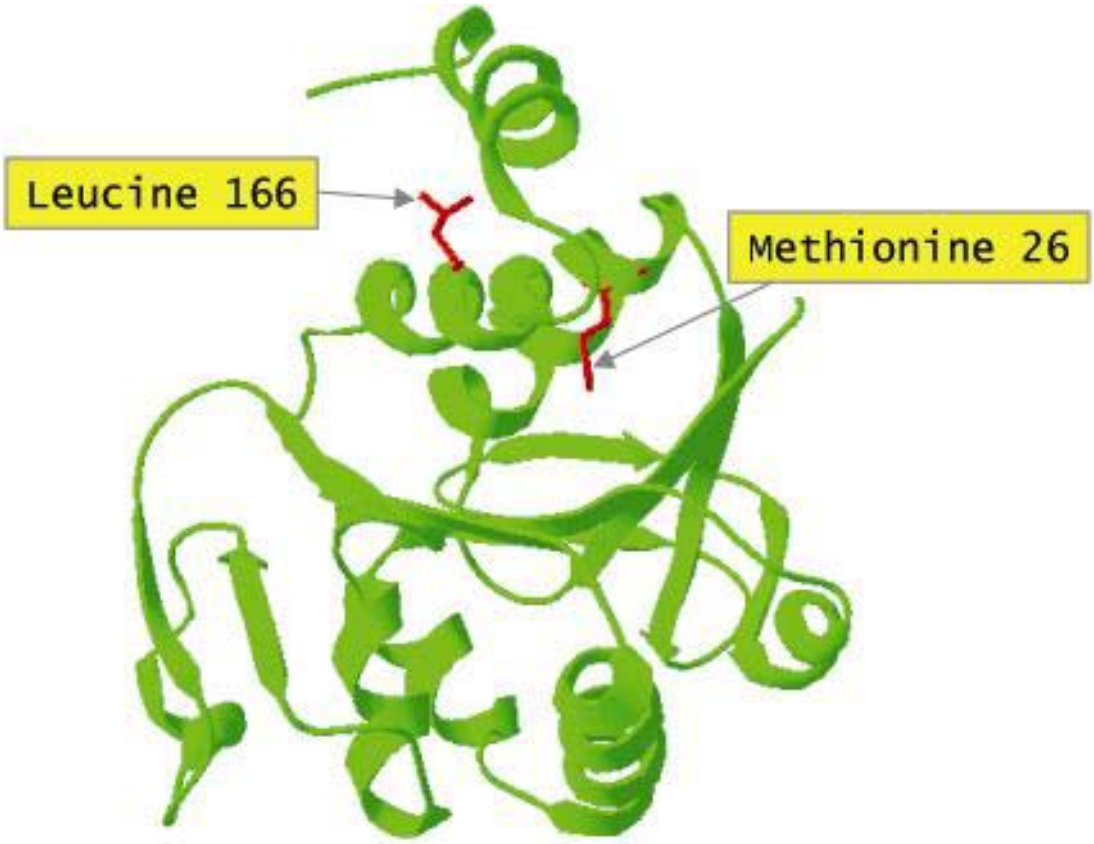

A model of the DJ-1 protein and the location of two identified mutation sites. Leucine 166 is mutated to proline in an Italian family (Bonifati, 2003) and methionine 26 is changed to isoleucine in a Ashenazi Jewish patient (Abou-Sleiman, 2003). Although the individual amino acids, shown here in red, are separated on the primary sequence, folding of the protein means that they are quite close together on the 3D structure. It is not yet clear whether additional mutations will be found or whether they will cluster together like this.